New Claim 33 specifies that the oligonucleotide is a peptide nucleic acid. Support may be found on page 14, lines 1 to 9 of the specification.

New Claim 34 specifies that the oligonucleotide comprises a morpholino backbone structure. Support may be found on page 14, lines 12 to 13 of the specification.

New Claim 35 relates to an oligonucleotide comprising at least one modified base. Support may be found on page 12, lines 19 to 27 of the specification.

New Claim 36 relates to an oligonucleotide comprising a modified phosphate backbone. Support may be found on page 14, lines 18 and 19 of the specification.

New Claim 37 relates to an oligonucleotide comprising one or more phosphorothioate internucleotide linkages. Support may be found on page 13, lines 9 to 13.

New Claim 38 is directed to intersugar linkages. Support may be found on page 13, lines 4 to 7.

New Claim 39 specifies that the oligonucleotide comprises at least one 2'-O-substituted ribonucleotide. Support may be found on page 13, lines 14 to 24 of the specification.

New Claim 40 is directed to a nuclease resistant oligonucleotide. Support may be found on page 14, lines 14 to 21 of the specification.

New Claims 41 and 42 are directed to a vector comprising an oligonucleotide of 20 to about 100 nucleotides in length or consisting of a sequence selected from the group of SEQ ID Nos: 1-30. Support may be found throughout the specification as filed, for

example on page 23, lines 8 to 10 and on page 36, lines 21 to 23. Support for the length of the oligonucleotide and the sequence is provided as mentioned above.

New Claims 43 and 44 relate to a pharmaceutical composition comprising an oligonucleotide of 20 to about 100 nucleotides in length or consisting of a sequence selected from the group of SEQ ID Nos: 1-30. Support may be found on page 25, lines 21 to 23. Support for the length of the oligonucleotide and the sequence is provided as mentioned above.

New Claims 45 and 46 recite various types of cancer. Support for this amendment can be found in Examples 1 to 4, and in Figures 1(a to f), 2(a and b), 3 and 4.

New Claims 47 to 51 are directed to a method for inhibiting colon tumor growth. Support may be found throughout the specification, for example, page 35, line 17, page 26, line 11 to 13, Table 1 and Example 3. Support for the chemotherapeutic drug may be found on page 36, line 3 to 5. Support for the oligonucleotide may be found as provided above.

New Claims 52 to 56 relate to a method for inhibiting metastasis of melanoma. Support may be found, for example, in Example 4 of the specification. Support for language directed to the use of a chemotherapeutic agent is as indicated above. Finally, support for language directed to the oligonucleotide is also as indicated above.

New Claims 57 and 58 are directed to methods comprising administering the oligonucleotide by infusion. Support may be found throughout the specification.

New Claims 59 to 61 are directed to methods, wherein the oligonucleotide consists of a sequence selected from the group of SEQ ID NOs:1-30. Support is as indicated above.

The foregoing amendments are made without any intention to abandon the subject matter of the claims as filed, but with the intention that claims of the same, lessor, or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. The Applicant asserts that no new matter has been added by way of these amendments. The Examiner's bases for rejecting claims 1-19, 23-25 and 30 are addressed below.

Rejection of Claims under 35 U.S.C. § 112, First paragraph (Enablement)

The Examiner has rejected Claims 6-16, 23-25 and 30 under 35 U.S.C. §112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the Office Action mailed January 15, 2003, Paper No. 28. The rejection is newly applied to Claims 6-16, 23-25 and 30.

Applicant acknowledges with thanks the Examiner's statement that the specification is enabling with regard to the antisense oligonucleotides of the invention for the *in vitro* inhibition of human cancer cell growth. Applicant further acknowledges with thanks the Examiner's comments that the instant disclosure is also enabling for the *in vivo* inhibition of human colon tumor growth and for the *in vivo* inhibition of metastasis of melanoma, using the antisense oligonucleotides of the invention.

The Examiner, however, alleges that the instant disclosure is not enabling for the antisense oligonucleotides of the invention for the inhibition of tumor growth, metastasis and neovascularization. Applicant respectfully traverses, and obviates-in-part, this objection.

Applicant maintains for reasons set forth in Responses filed on March 28, 2001, April 29, 2002 and June 16, 2003, that the Specification is fully enabling for a method of inhibiting the neovascularization of human cancer cells *in vitro* and *in vivo* using

antisense oligonucleotide directed against a neuropilin gene. In order to expedite examination however, Applicant has withdrawn claims 14 to 16.

With regard to claims 6-13, 23-25 and 30, Applicant maintains for the reasons set forth in Responses filed on March 28, 2001, April 29, 2002 and June 16, 2003, that the specification is fully enabling for methods of inhibiting the growth and metastasis of human cancer cells *in vitro* and *in vivo* using antisense oligonucleotides directed against a neuropilin gene. Applicant reiterates that one skilled in the art would have a reasonable expectation that the *in vitro* and *in vivo* examples provided in the specification would correlate with full scope of claims. As stated at MPEP 2164, "The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent with information known in the art without undue experimentation." In order to be enabling, the specification must simply demonstrate that the invention works as claimed and provide sufficient guidance to allow one skilled in the art to make and use the invention as claimed.

Contrary to the Examiner's suggestion, Applicant's arguments in the Response dated June 16, 2003 address far more than the existence of antisense oligonucleotides in clinical trials for targets other than neuropilin. In fact, Applicant has provided evidence in the Examples of the specification which demonstrate that antisense oligonucleotides of the invention directed against neuropilin, have *in vitro* efficacy and that such *in vitro* efficacy has been correlated to *in vivo* efficacy. Moreover, Applicant has previously provided evidence that the murine xenograft model used to demonstrate *in vivo* efficacy was at the time of the application, an art recognized model and good predictive tool for clinical efficacy and that this is sufficient to meet the requirements for enablement. Reference to other clinical trials for antisense therapies, serves as yet further evidence that such murine models are in fact predictive of clinical efficacy. Accordingly, it is Applicant's assertion that a person skilled in the art could, without undue experimentation, work the invention over the full scope of the claims.

In order to expedite examination, however, Applicant has amended independent claims 6 and 10 to recite that the tumor targeted by the antisense oligonucleotides of the invention is a carcinoma, as supported and fully enabled by the Examples of the specification, demonstrating the efficacy of the claimed antisense oligonucleotides in a variety of carcinomas, as further listed in new dependent claims 45 and 46.

In addition, in order to clarify the subject matter of Claims 23 to 25, Applicant has amended Claim 23 to recite a method of inhibiting the growth of human cancer cells *in vitro*.

Accordingly, Applicant asserts that Claims 6-13, 23-25 and 30 meet the requirements of §112, first paragraph. The Applicant respectfully requests reconsideration and withdrawal of this rejection and reserves the right to pursue the withdrawn subject matter in the present application or in a continuation, continuation-in-part, or a divisional application.

Rejection of Claims under 35 U.S.C. § 103(a) (Obviousness)

The Examiner has rejected Claims 1, 4, 5, 23 and 25 as being unpatentable over He *et al.* and Soker *et al.*, the combination in view of Milner *et al.* and Baracchini *et al.* alleging that it would be obvious to one of ordinary skill in the art to inhibit the expression of SEQ ID NO:33 using antisense olignucleotides *in vitro* because the nucleotide sequence of human neuropilin has been taught previously by He *et al.* and this gene has been implicated in the proliferation of cell growth, including cancer cell growth, as apparently taught by Soker *et al.* Furthermore, the Examiner alleges that Milner *et al.* taught methods for designing and testing antisense olignucleotides, suggesting that one of

ordinary skill in the art would have expected that antisense between 15 and 100 nucleobases that are targeted to SEQ ID NO:33 would inhibit its expression *in vitro.* Additionally, the Examiner relied on Baracchini *et al.* for teaching that phosphorothioate internucleotide modifications to antisense oligonucleotides enhances antisense stability and target binding, as well as teaching that the administration of pharmaceutical compositions comprising antisense oligonucleotides to appropriate cells *in vitro* inhibits target gene expression and target cell growth. It is also the Examiner's belief that it would have been obvious to administer a vector encoding antisense targeting human neuropilin to inhibit the target's gene expression since the use of vectors for expression in cells is routine in the art. Applicant respectfully traverses this rejection.

The Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, (1) there must be some suggestion or motivation to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations (MPEP § 2143). With regard to the instant claims, Applicant respectfully submits that the Examiner has failed to discharge his burden of factually supporting any *prima facie* conclusion of obviousness. The cited references, alone or in combination with each other, do not suggest or motivate an ordinary worker skilled in the art to combine or modify the reference teachings. Furthermore, the prior art does not teach or suggest all the claim limitations. Accordingly, the cited prior art would not lead a person of ordinary skill in the art to have a reasonable expectation of success.

A. Prior art does not suggest or motivate to combine references

Applicant respectfully submits that based on a reading of He *et al.* and Soker *et al.*, a person of ordinary skill in the art would not have combined these references to conclude that the subject matter of claims 1, 4, 5, 23 and 25 is obvious.

He *et al.* discloses a human neuropilin homolog in the context of elucidating the mechanism by which the Sema III-binding protein mediates its effect on axons of the developing nervous system. There is nothing in He *et al.*, which predates Milner *et al.*, that suggests a link between the receptor neuropilin and VEGF or a link between neuropilin and tumor formation.

Furthermore, Applicant respectfully submits that the Examiner's statement that Soker *et al.* teaches that high levels of neuropilin have been noted in various types of tumors is incorrect. Contrary to the Examiner's statement that neuropilin is also known as $VEGF_{165}$, neuropilin (a receptor) and $VEGF_{165}$ (a ligand) are in fact distinct proteins. Soker *et al.* only conclude that high levels of VEGF, and not its receptors, are associated with tumor formation (see page 5761, 2nd paragraph on right). With respect to the VEGF receptors, VEGF was demonstrated to bind to the known receptor tyrosine kinases KDR and FLT and, with lower affinity, to a newly discovered receptor with a lower molecular mass. At the time of this article, however, this lower affinity/molecular mass VEGF receptor had yet to be purified and characterized. Its structure and role in modulating VEGF activity was not known at the time of publication (page 5766, first sentence in last paragraph on left and summary paragraph on right). There is nothing in Soker *et al.* that would lead a person skilled in the art to reasonably expect that inhibition of the expression of the new receptor identified therein would result in the inhibition of cancer cell growth. Accordingly, a skilled person would not consider this new receptor to be a suitable therapeutic target.

In *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 6562 (CCPA 1972), the Court held that "[i]n determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." Applicant respectfully submits that this was not the case in the present

situation since there is nothing in the cited prior art that teaches or suggests that neuropilin is even a receptor for VEGF or that neuropilin is associated with tumor growth. Moreover, contrary to the Examiner's assertion, one of ordinary skill in the art would not have been motivated to inhibit the expression of human neuropilin of SEQ ID NO:33 because the possible modulating function of this gene was not known with respect to cancer cell growth. This function is not evident from He *et al.* or Soker *et al.* when considered alone or in combination. Accordingly, Applicant respectfully submits that the Examiner has not successfully discharged his burden of showing that a skilled artisan would have combined the teaching of He *et al.* with Soker *et al.* along with Milner *et al.* or Baracchini *et al.* to address the problems that are solved by the instant application relating to the design and application of antisense against neuropilin.

B. Prior art does not teach or suggest all claim limitations

When determining if a *prima facie* case of obviousness has been established, "all the claim limitations must be taught or suggested by the prior art" (*In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). This is done by considering all the words in a claim when judging the patentability of that claim against the prior art (*In re Wilson,* 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

In the instant application, independent claim 1 and related claims 4, 5, and 23 recite a sequence from about 15 to 100 nucleotides comprising at least 15 consecutive nucleotides with a sequence complementary to a human neuropilin mRNA, wherein said mRNA has a sequence as set forth in SEQ ID NO:33, and wherein the oligonucleotide specifically binds to a nucleic acid comprising a sequence corresponding to said mRNA and inhibits neuropilin expression in a human.

The Examiner alleges that it would be obvious to a person of ordinary skill in the art to expect antisense oligonucleotides designed and assessed according to the method

taught by Milner *et al.* to be successfully used for the *in vitro* inhibition of neuropilin expression and consequently the inhibition of cell growth *in vitro* since neuropilin had been implicated in the proliferation of cancer cell growth. As discussed previously, however, there is nothing in He *et al.* or in Soker *et al.* when considered alone or in combination, that teaches or suggests that inhibiting the expression of the mRNA of SEQ ID NO:33 would result in the inhibition of tumor cell growth. As such, one skilled in the art would not have been motivated to apply Milner to design of antisense oligonucleotides directed against the mRNA of SEQ ID NO. 33.

Finally, the Examiner alleges that Baracchini *et al.* teach the administration of pharmaceutical compositions comprising antisense oligonucleotides to appropriate cells *in vitro* to inhibit target gene expression and target cell growth, as well as teaching the incorporation of phosphorothioate internucleotide linkages into antisense oligonucleotides. Applicant, however, respectfully submits that nothing in Baracchini cures the fundamental defects of He *et al.*, Soker *et al.* or Milner *et al.* taken alone on in combination, as discussed above. Barachini does not suggest the instantly claimed antisense oligonucleotides, pharmaceutical compositions, vectors, nor their use to inhibit neuropilin expression in a human.

In summary, therefore, Applicant respectfully submits that the prior art references when combined do not teach or suggest all the claim limitations of claims 1, 4, 5, 23 and 25.

C. No reasonable expectation of success

MPEP 2143.02 states that obviousness requires some degree of predictability, which must be determined at the time the invention is made. In the present case, it is Applicant's assertion that the prior art would not have created a reasonable expectation of success with regard to the antisense oligonucleotides of the present invention.

Again, for reasons previously stated, the cited prior art would not have lead a worker skilled in the art to conclude that neuropilin had a modulating activity with regard to cancer cell growth. Furthermore, contrary to the Examiner's assertion that Milner *et al.* teaches methods for designing and testing antisense oligonucleotides, Milner *et al.* only provides a combinatorial time-saving technique that allows for simultaneous assessment of all possible oligonucleotides within a given region in order to identify sequences open to duplex formation. According to Milner *et al.*, the process is a simple empirical method that requires other preliminary data to identify sequences that may be amenable to heteroduplex formations (at page 540, last full sentence).

According to Milner, oligonucleotides that give high duplex formation yield are also effective antisense agents in *in vitro* RNase H and translation studies (Milner *et al.* at page 537, 2nd and 3rd paragraphs on left). Although Milner pointed to a possible association between open regions and a high incidence of duplex formation, there was nothing taught or suggested that would lead a person of ordinary skill in the art to easily select the region of mRNA to test for duplex formation. Sequences and predicted secondary structures of the mRNA of interest provided few clues as to the regions that are open to duplex formation (at page 539, 1st paragraph in Discussion regarding figure 2). Significant experimentation and inventive ingenuity would still be required to develop antisense oligonucleotides capable of inhibiting targets other than the one specifically examined by Milner *et al.* Accordingly, Applicant respectfully submits that the combination of He *et al.*, Soker *et al.*, and Milner *et al.* is insufficient to direct a person of ordinary skill in the art to design and test the antisense oligonucleotides of the present invention on the basis of a reasonable expectation of success.

For the reasons discussed above, Applicant respectfully submits that the Examiner has not set forth a *prima facie* case of obviousness, and Applicant requests reconsideration and withdrawal of this rejection.

Rejection of Claim under U.S.C. §112, second paragraph (Indefiniteness)

The Examiner has objected to Claim 3 as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. It is the Examiner's assertion that the metes and bounds of the phrase 'additional nucleotides not complementary to the neuropilin mRNA' cannot be determined in Claim 3, and therefore appropriate clarification is requested.

Applicant respectfully submits that a person skilled in the art would fully appreciate the metes and bounds of Claim 3. Applicant respectfully reminds the Examiner that the claims are directed to a worker skilled in the art having regard to the specification and asserts that one skilled in the art would understand the metes and bounds of the phrase "additional nucleotides not complementary to the neuropilin mRNA'. On pages 23 and 36, Applicant provides examples of such nucleotides, which include expression elements such as transcription and translation control sequences and reporter genes linked to the antisense oligonucleotide for use in vectors. Additional examples include promoters and regulatory sequences, support for which may be found on page 37.

In the specification, Applicant has provided examples of additional nucleotides that are not complementary to the neuropilin mRNA, but linked to the claimed oligonucleotide for various uses that are well known in the art. Furthermore, the oligonucleotide of the present invention may also be used as a primer in hybridization probes (page 38). Accordingly, it is well known in the art that additional nucleotides, such as restriction sites and linkers, may be ligated to the ends of the primer where necessary. However, in order to expedite prosecution of the instant application, Applicant has withdrawn Claim 3. Applicant asserts that this amendment was made for reasons of clarity and not for reasons of patentability. Applicant reserves the right to

pursue the withdrawn subject matter in a continuation, continuation-in-part, or divisional application. Accordingly, Applicant respectfully requests withdrawal of this objection under 35 U.S.C. §112, second paragraph.

Rejection of claims under 35 U.S.C. 112, first paragraph

The Examiner has rejected Claims 1-19, 23-25 and 30 as containing subject matter that was not described in the specification in such a way so as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, the Examiner alleges that the specification and claims do not indicate the distinguishing attributes that are essential to the genus comprising antisense oligonucleotides or analogs thereof, or optionally further comprising additional nucleotides not complementary to SEQ ID NO:33. Thus, the scope of the claims includes significant number of structural variants. It is the Examiner's contention that concise structural features that could distinguish structures of compounds within these genera from others are missing from the disclosure. As a result, this would lead a person skilled in the art to conclude that the disclosure fails to provide a representative number of species to describe the genera claimed.

Applicant respectfully traverses. MPEP 2163 states that in order to satisfy the written description requirement, a patent specification must "describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Possession can be shown by describing the claimed invention "using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." The Applicant respectfully submits that as discussed *supra* the specification as filed provides detailed teaching regarding the selection of the claimed antisense oligonucleotide from all other oligonucleotides. Furthermore, Applicant asserts that this description of the antisense oligonucleotides along with the disclosed methods of testing antisense oligonucleotides

(*See* Examples section of the Specification) clearly demonstrate how a person skilled in the art may distinguish between the oligonucleotide of the present invention from others without undue experimentation. However, in order to expedite examination, Applicant has withdrawn Claim 3 and has amended Claims 1, 4, 5, 6, 10, 14, 17, and 23 such that they no longer refer to an analog or additional nucleotides that are not complementary to the neuropilin mRNA.

Applicant reserves the right to pursue the withdrawn subject matter in a continuation, a continuation-in-part, or a divisional. In view of the present remarks and amendments, Applicant respectfully submits that Claims 1-19, and 23-25 meet the requirements of 35 U.S.C. §112 and respectfully requests that the Examiner withdraw this objection.

CONCLUSION

On the basis of the foregoing claim amendments and remarks, Applicants respectfully submit that, upon entry, the pending claims will be in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Enclosed is Check No. 554899 in the amount of $475.00 for the fee for Three (3) Months extension of time. The Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 50-1355. A copy of this Petition Sheet is enclosed.

Respectfully submitted,

Date: February 26, 2004

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